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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,953	10/03/2000	Hiroshi Kubota	113918,401	7343

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EXAMINER
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ART UNIT	PAPER NUMBER
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/678,953	KUBOTA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-26 are pending.

Claims 1-20, 25 and 26 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I (Claims 1-20, 25 and 26) in Paper No. 11, is acknowledged. The traversal is on the ground(s) that the examination of all the claims 1-26 would not be a serious burden to the Examiner, particularly because the Examiner has not provided reason as to why the examination of all claims would be a serious burden. This is not found persuasive because the Examiner has shown that the composition and methods of gene therapy of Invention I are mutually exclusive and independent from the methods of obtaining a mixture of cells enriched in progenitors and methods of identification of progenitors cells of Invention II. Inventions can be shown to be distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the bipotent hepatic progenitor cells of Invention I can be obtained by different methods than the methods described in Invention II, for example, the cells can be hand-sorted using confocal microscopy and detection methods well-known in the art. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

Claims 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11 (Filed 12/4/01).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising bipotent hepatic progenitors which express intercellular adhesion molecule-1 (ICAM-1) and do not express major histocompatibility complex (MHC) class Ia antigen, in which the bipotent hepatic progenitors have the capacity to differentiate into either hepatocytes or biliary cells *in vitro*, and the hepatic progenitors express a dull positive in fluorescence-activated cell sorting (FACS) for at least one MHC class IB antigen, the specification does not reasonably provide enablement for methods of treating a liver disorder or dysfunction with liver progenitors in a subject in need thereof, comprising administering to the subject an effective amount of cells enriched in human liver progenitors in a pharmaceutically acceptable carrier, in which the human liver progenitors express an ICAM antigen and do not express MHC class Ia antigen, or a method of treating a genetic disorder in an individual in need thereof comprising administration of an effective amount of a bipotent hepatic progenitor harboring a gene which corrects a

genetic disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a composition comprising bipotent hepatic progenitors which express at least one ICAM antigen and do not express MHC class Ia antigen, where the bipotent hepatic progenitors have the capacity to differentiate (claims 1-20). In further embodiments, the claimed invention is directed to methods of treating a liver disorder or dysfunction with liver progenitors in a subject in need thereof, comprising administering to the subject an effective amount of cells enriched in human liver progenitors in a pharmaceutically acceptable carrier, in which the human liver progenitors express an ICAM antigen and do not express MHC class Ia antigen, or a method of treating a genetic disorder in an individual in need thereof comprising administration of an effective amount of a bipotent hepatic progenitor harboring a gene which corrects a genetic disorder (claims 25-26).

The specification teaches that novel cell surface markers can be used to distinguish hepatic cells from hemapoietic cells, and in particular, the specification teaches methods of isolating bipotent hepatic progenitor cells with a unique phenotype, which are negative for MHC Class I antigen, positive for ICAM-1 and dull positive for nonclassical MHC class I antigens. The specification teaches that a cell population enriched in hepatic progenitors can be obtained, and then separated by methods such as flow cytometry, affinity methods with antibodies, etc (see p. 6, lines 24-30). The specification teaches that using ICAM-1 and classical MHC negative markers, bipotent

cells can be sorted. For example, hematopoietic, mesenchymal and mature hepatic cells express both ICAM-1 and MCH class Ia, whereas in rat fetal liver, classical MHC class I negative cells include bipotent hepatic progenitors and enucleated mature erythrocytes (see p. 10, lines 10-24). In particular, the specification teaches that fetal rat livers were obtained and prepared from day 15 gestation and the cells cultured. After 4 weeks of culture, the cells were cultured on a feeder layer of mitomycin C-treated STO mouse embryonic fibroblast line (see p. 14, Example 6.1). Immunohistochemical analysis of alpha-fetoprotein and albumin were performed in continuous growing cell populations before the cloning of cell lines, to confirm that the cell populations originated from hepatic lineage, and several stable hepatic cell lines were established (see Example 6.2). To develop a colony forming assay to identify bipotent hepatic progenitors with high growth potential, the culture system must be able to support cell expansion at clonal seeding densities, therefore STO subclones were isolated for the colony formation (Example 6.3) and hepatic progenitors from E13 fetal liver were identified using surface antigenic markers (MHC class I and ICAM-1) by fluorescent activated cell sorting and screening of the sorted cells for clonal growth potential (see Example 6.4). The specification teaches that by choosing antibodies specific for ICAM-1 in a specific species and antibodies for a designated class I MHC antigen, cell populations enriched in hepatic progenitor cells can be isolated (see Example 6.7). The specification discusses the use of the liver progenitor cells identified by the claimed method in *ex vivo* gene therapy (see pp. 31-34), in diseases such as

phenylketonuria, and for use in therapy in a rat liver model of liver failure to evaluate heterogeneous cell transplantation therapy (see p. 33, Example 6.17).

The specification teaches that the isolation of hepatic progenitor cells with high growth potential is an art-recognized problem, and that hepatic progenitor cell cultures are often contaminated with other cell types such that insufficient amounts of true hepatic progenitor cells are present, and even those that are present do not grow well, or differentiate enough for therapy. The specification teaches that bipotent hepatic progenitors do not express classical MHC class I antigens, and do express ICAM-1 antigens (note that ICAM-1 is used to designate the form of ICAM molecules found in mammals, see p. 12, lines 16-17), and as such, the specification teaches a method for identification of these bipotent hepatic progenitor cells by detection of the MHC class I phenotype in combination with ICAM-1 expression (see p. 7, lines 8-13). Furthermore, the specification teaches hepatic precursors can be further isolated by their "dull" expression (i.e., intermediate intensity of fluorescence during FACS) of nonclassical MHC class I antigens (see p. 29, lines 1-2). As such, the scope rejection of the claimed invention reflects the cellular markers identified in the specification with the bipotent hepatic progenitor cells disclosed. Accordingly, in view of the teachings of the specification, it would not be predictable as to which other cell markers would be functional in the claimed method of isolating hepatic progenitor cells, other than the disclosed markers of MHC class I antigen, ICAM-1 expression and MHC class Ib dull expression.

Furthermore, the claimed methods encompass cellular transplantation. However, many unpredictable factors complicate cellular transplantation. Inverardi *et al.* (**Transplant Biology**, 1996) review the state of the art of cell transplantation and discuss various factors that affect successful cellular transplantation, such as problems of cell isolation and purification, cellular environment, the immune response to transplanted cells, as well as the preservation of cells used in cellular transplantation (see pp. 679-681). Inveradi *et al.* further review various clinical applications for cellular transplantation, each with varying results (see pp. 681-684). Inverardi *et al.* discuss the genetic engineering of cells to be used in cellular transplantation, and discuss the limitations of currently available gene delivery systems (see p. 685). Additionally, Saadi & Platt (**Life Sciences**, Vol. 62, No. 5, pp. 365-387, 1998) review the state of the xenotransplantation, which often leads to a variety of immune responses. Various factors need to be considered for xenotransplantation, including the selection of a donor species and the transplant's compatibility with the recipient, which could induce cellular or humoral rejection (see Figure 1, p. 367). Furthermore, Saadi & Platt state that susceptibility of rejection of various tissues and organs are dependent upon the particular tissue or organ used in the transplant (See p. 369). Saadi & Platt conclude that, with regard to xenotransplantation, "Thus, it is not possible to predict that xenotransplantation will enter the clinical arena in a very few years." (See p. 381).

In general, *in vitro* gene expression is not representative of gene expression in a host subject whose cells (or target cells) have been somatically transfected *in vivo*. This is because numerous factors complicate *in vivo* gene transfer and expression which

result in therapeutic effects. See Eck & Wilson ('Gene-Based Therapy' in The Pharmacological Basis of Therapeutics, 1996), who report that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See page 82, column 1, first paragraph. These factors differ dramatically based on the vector used, the route of administration of the vector, the protein being produced, which cells are the target cells, and the disease and/or host being treated. It is further noted that Eck and Wilson support the importance of tailoring a gene therapy vector and method to specific diseases and/or disorders. See page 82, column 1, first paragraph. For example, Eck & Wilson et al. review the state of the art for gene therapy for inherited disorders and discloses that "[t]he level of protein function necessary to achieve complementation of the defect varies widely among genetic diseases." See page 78, column 2, 2nd paragraph

Further, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient

as supported by numerous teachings available in the art. Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

The specification fails to teach the amount of hepatic progenitor cells necessary to achieve therapy in any individual suffering from a liver disorder or dysfunction. The specification fails to address how to overcome any of the above described unpredictable parameters in the gene therapy art, such that one would be able to achieve therapeutic expression of a gene of interest for the breadth claimed, for any individual suffering from a liver disorder or dysfunction. As such, with respect to the unpredictable nature of the gene therapy art, and specifically when taken with the specification's lack of teaching or sufficient guidance for *ex vivo* gene therapy using hepatic progenitor cells which express ICAM-1 and do not express MHC class Ia antigen, it is not predictable if a gene

of interest's expression would start or continue in the targeted cells for a duration that would be considered therapeutic in a subject suffering from liver disease, as somatic gene therapy often results in very limited expression, in an inadequate number of cells.

Note further that cited art clearly indicates the unpredictable status of the gene therapy art. Although specific vectors, promoters, genes and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy, as a broad-based art, is clearly unpredictable in terms of achieving levels of duration and expression of a particular gene of interest which results in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed. In the instant application, a correlation cannot be drawn for the reasons discussed in the preceding paragraphs. As established by the state of the art of gene therapy, note that therapeutic expression is not an inherent feature in methods of either *in vivo* or *ex vivo* gene transfer involving expression of a protein of interest. In fact, the lack of a therapeutic response in many gene therapy protocols contributes to the unpredictable and undeveloped status of the art of gene therapy.

Note also, that the issue of "correlation" is dependent upon the state of the art at the time of the invention. MPEP 2164 discusses that if one skilled in the art cannot readily anticipate the effect of a change within a subject matter to which the claimed invention broadly pertains, then there is a lack of predictability in the art. Thus, what is known in the art provides evidence as to the question of predictability.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving *ex vivo* gene therapy using hepatic progenitor cells which express ICAM-1 and do not express MHC class Ia antigen by any mode of administration, the lack of direction or guidance provided by the specification to carry out *ex vivo* hepatic progenitor gene therapy, and the unpredictable and undeveloped state of the gene therapy art, it would have required undue experimentation for one skilled in the art to carry out the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written, is confusing. Line 1 of the claim states, "At least" (with a capital "A") it is suggested that this be written "at least" for clarity. Furthermore, the claim recites, "bipoint" in line 3 of the claim. It is suggested that this be written, "bipotent". Clarification and/or amendment is requested. Claims 1-13 depend from claim 1.

Claims 3 and 14 recite the term, "weakly." It is not clear what this term encompasses. Clarification and/or amendment is requested. Claims 15-20 depend from claim 14.

Claim 5 recites the term, "less than." It is unclear what this term encompasses. Clarification and/or amendment is requested.

Claim 14 recites the term, "higher" in part (b) of the claim. It is unclear what the term, "higher" encompasses. Clarification and/or amendment is requested.

Claim 25, as written, is incomplete. It is unclear how administering to a subject an effective amount of cells enriched in human liver progenitors in a pharmaceutically acceptable carrier, in which the human liver progenitors express an ICAM antigen and do not express MHC class Ia antigen, relates to the preamble, "A method of treating a liver disorder or dysfunction." Clarification and/or amendment is requested.

Conclusion

Claims 1-20, 25 and 26 appear to be free of the prior art of record because the cited prior art of record fails to teach or suggest a composition comprising bipotent hepatic progenitors which express at least one ICAM antigen and do not express MHC class Ia antigen, where the bipotent hepatic progenitors have the capacity to differentiate (claims 1-20). In further embodiments, the claimed invention is directed to methods of treating a liver disorder or dysfunction with liver progenitors in a subject in need thereof, comprising administering to the subject an effective amount of cells enriched in human liver progenitors in a pharmaceutically acceptable carrier, in which

the human liver progenitors express an ICAM antigen and do not express MHC class Ia antigen, or a method of treating a genetic disorder in an individual in need thereof comprising administration of an effective amount of a bipotent hepatic progenitor harboring a gene which corrects a genetic disorder (claims 25-26). However, the claims are subject to other rejections.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Crouch, Acting Supervisory Primary Examiner of Art Unit 1632, at (703) 308-1126. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

TNT

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